REMARKS

Claim Amendments

Claims 45-48, 50-51 and 53-54 are pending herein. Claims 47 and 53 have been amended herein to more clearly point out that which Applicants regard as the invention. No new matter has been added.

Telephonic Interview

Applicants would like to thank Examiner Vakili and Supervisory Patent Examiner Marschel for participating in the telephonic interview on June 25, 2009. The comments herein reflect the discussion of the Office Action during the interview.

Rejection of Claims 45-48, 50-51 and 53-54 Under 35 U.S.C. §112, First Paragraph

Claims 45-48, 50-51 and 53-54 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement because, according to the Office Action, the claims are directed to encompass small molecules that only correspond in some undefined way to the instantly disclosed agent. However, the Office Action goes on to state that the specification discloses a method for modulating cell proliferation of a cell comprising inhibiting specific histone deacetylase (HDAC) isoforms that is involved in cell proliferation with an agent that inhibits one or more specific deacetylase isoforms [but less than all], which **meets** the written description and enablement provisions of 35 USC 112, first paragraph (emphasis added).

Applicants believe that this apparent inconsistency results from the Office Action's continued examination of the claims as being directed to antisense oligonucleotides as evidenced by the reliance on Fiers v. Revel, 25 USPQ2d 1601 (CAFC 1993), Baird, 30 USPQ2d 1481 and University of California v. Eli Lilly and Co., 43 USPQ2d 1398.

However, Applicants direct the Examiner to University of Rochester v. G.D. Searle & Co., 358 F.3d 916 (Fed Cir. 2004) and Ariad Pharmaceuticals, Inc. v. Eli Lilly and Company, 560 F.3d 1366 (Fed. Cir. 2009) which are on point. A representative claim at issue in the Rochester case is as follows:

> 1. A method for selective inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment.

In the Rochester case, the district court found, and the Federal Circuit agreed, that, "although all of the claims require the use of a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene, the '850 patent neither discloses any such compound nor provides any suggestion as to how such a compound could be made or otherwise obtained other than by trial-and-error research. Id. at 919. Indeed, the court found no evidence in the '850 patent that the inventors themselves knew of any such compound at the time their patent application was filed. Id. at 919. Accordingly, the court conconcluded that the patent's claims are invalid for lack of written description. Id. at 919."

The Ariad case involved gene regulation technology, specifically by reducing activity of the transcription factor NF-κB. A representative claim at issue in the Ariad case, rewritten to include the claim from which it depends, is as follows:

> 95. [A method for reducing, in eukaryotic cells, the level of expression of genes which are activated by extracellular influences which induce NF-κB-mediated intracelluar signaling, the method comprising reducing NF-κB activity in the cells such that expression of said genes is reduced], carried out on human cells.

In the Ariad case, the Federal Circuit stated that:

> "…to satisfy the written description requirement for the asserted claims, the specification must demonstrate that Ariad possessed the claimed methods by sufficiently disclosing molecules capable of reducing NF-κB activity…"

As stated in the Ariad case, the specification of the Ariad patent (the '516 patent) merely hypothesized three classes of molecules potentially capable of reducing NF-κB activity: specific inhibitors, dominantly interfering molecules, and decoy molecules. Thus, the Federal Circuit concluded that the asserted claims were invalid because:

> "The '516 patent discloses no working or even prophetic examples of methods that reduce NF-κB activity, and no completed synthesis of any of the molecules prophesized to be capable of reducing NF-κB activity".

This, however, is simply not the case in the instant application. As indicated in paragraph [0010], of the application as published, all of the previously known inhibitors of histone deacetylase are non-specific for a particular histone deacetylase isoforms, i.e., they are pan-

inhibitors. As further indicated in paragraph [0013], the inventors have discovered new agents that inhibit specific HDAC isoforms. Representative examples of small molecule inhibitors are presented in the specification (Table 2, page 7).

Moreover, examples 8-13 and Table 2 teach the structures and uses of small molecule inhibitors that inhibit some isoforms but less than all isoforms and examples 14-16 teach how they were synthesized. Further, example 11 and Table 2 indicate that such compounds inhibit tumor formation *in vivo*. Thus, the specification discloses working examples of compounds that can be used in the instantly claimed method; teaches how the compounds can be made and provides examples that one skilled in the art would be able to use to determine whether or not a small molecule is an inhibitor of some isoforms but less than all isoforms. Specifically, paragraphs [0111] and [0153]-[0158] provide the skilled artisan with the ability to identify a particular small molecule inhibitor as one that will inhibit more than one specific histone deacetylase isoforms but less than all isoforms. Therefore, as Applicants provide examples of small molecules that inhibit some but less than all HDAC isoforms, teach how this characteristic is to be identified, and demonstrate that they possessed the claimed methods by sufficiently disclosing molecules capable of performing the claimed methods, the specification satisfies the written description requirement. Reconsideration and withdrawal are respectfully requested.

Rejection of Claims 47, 48, 53 and 54 Under 35 U.S.C. §112, Second Paragraph

Claims 47, 48, 53 and 54 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the instant claims are rejected for lacking clear antecedent basis.

Claims 47 and 53 have been amended herein to distinctly claim the subject matter which Applicants regard as the invention. Specifically, Claims 47 and 53 recite that the small molecule inhibitor inhibits one or more specific histone deacetylase isoforms ~~is~~ selected from the group consisting of HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7 and HDAC-8, but less than all histone deacetylase isoforms. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 45-48 Under 35 U.S.C. §102(b)

Claims 45-48 are rejected under 35 U.S.C. §102(b) as anticipated by Jones et al. (Nature Genetics, 1998, of record). According to the Office Action, Jones et al. disclose contacting a cell with TSA, a small molecule inhibitor of histone deacetylase (HDAC). However, TSA is a pan-inhibitor (i.e., it is non-specific) and inhibits **all** HDAC isoforms.

Claims 45-48 recite that the agent is a histone deacetylase small molecule inhibitor which inhibits one or more specific histone deacetylase isoforms but less that all (i.e., a non-pan-inhibitor), which is not taught by Jones et al. Therefore, Jones et al. fails to anticipate Claims 45-48. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 45-48, 50-51 and 53-54 Under 35 U.S.C. §102(b)

Claims 45-48, 50-51 and 53-54 are rejected under 35 U.S.C. §102(b) as being anticipated by Kwon et al. (Proc. Natl. Acad. Sci. USA 1998, vol. 95, pages 3356-3361). According to the Office Action, Kwon et al. disclose a small molecule inhibitor which inhibits histone deacetylase 1 (HDAC-1).

As argued in response to the previous Office Action, Kwon does not teach or suggest that depudecin inhibits "one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms". The Office Action continues to assert that HDAC-1 is the only isoform inhibited by Kwon; however, this is simply in error. While it is true that some of the assays only measure HDAC-1 activity as a marker to determine whether HDAC activity is inhibited, there is nothing which teaches that depudecin inhibits only HDAC-1. Rather, Kwon compares depudecin activity to trichostatin A and trapoxin activity, two pan-inhibitors of HDACs (i.e., inhibit all isoforms).

As taught by Kwon, depudecin shares common target proteins with trapoxin (see Kwon, "[^{3}H] Trapoxin Binding Assays" using extracts, pg 3358). Moreover, Kwon teaches that "it is known that inhibition of this activity by trichostatin A, trapoxin, and sodium butyrate results in the accumulation of hyperacetylated histone species." Kwon goes on to state that, as shown in Fig. 5, depudecin induces hyperacetylation of histones in a dose-dependent manner and that trichostatin A also strongly induces hyperacetylation of histones (see Kwon, "Depudecin induces Histone Hyperacetylation *in vivo*" using extracts, pgs 3358-3359. Finally, Figure 6A shows that in an assay testing the inhibitory activity of a compound against a total cellular extract of cellular

HDACs, depudecin inhibited the **total cellular** HDAC activity in a dose-dependent manner and that trichostatin A also showed strong inhibition (page 3359, left column, last paragraph; Figure 6A). No plateau for total cellular HDAC inhibition is demonstrated, taught or suggested in the Figure 6A or anywhere in the reference (i.e., if depudecin was inhibiting only HDAC1, one skilled in the art would expect a leveling off of inhibition demonstrated by activity of non-inhibited HDACs). Thus, the PTO cannot ignore the full teachings of the Kwon reference especially that several assays use crude cell extracts which measures total HDAC activity and not just HDAC1.

Therefore, one of skill in the art would expect that increasing the dose of depudecin would result in increasing in the inhibition of HDAC activity in the cell extract. In other words, from the teachings of Kwon et al., one of skill in the art would come to the conclusion that depudecin is a pan-inhibitor of HDACs. As such, Claims 45-48, 50-51 and 53-54 are not anticipated by Kwon. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 45-48 Under 35 U.S.C. §102(e)

Claims 45-48 are rejected under 35 U.S.C. §102(e) as being anticipated by MacLeod et al. (US 2003/0078216). According to the Office Action, MacLeod et al. disclose a method of inhibiting cell proliferation by inhibiting histone deacetylase using antisense oligonucleotides.

Applicants would like to point out that the instant claims are not directed to antisense oligonucleotides. Rather Claims 45-48, are directed to an agent that inhibits one or more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, wherein the agent is a histone deacetylase small molecule inhibitor. As such, Claims 45-48 are not anticipated by MacLeod. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 45-48 Under 35 U.S.C. §103(a)

Claims 45-48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Sambucetti et al., in view of Taunton et al., Baracchini et al., and Bennett et al.

Applicants again would like to point out that the instant claims are not directed to antisense oligonucleotides. Rather Claims 45-48, are directed to an agent that inhibits one or

more specific histone deacetylase isoforms, but less than all histone deacetylase isoforms, wherein the agent is a histone deacetylase small molecule inhibitor.

As would be clear to one skilled in the art, antisense are not small molecule inhibitors. Rather, these terms have clear and distinct meaning directed at two very difference classes of molecules. Antisense oligonucleotides are large molecules comprising several nucleotides linked together. One of skill in the art of antisense technology, in fact, will understand that a minimum of about 15 nucleotides would be required for a functional antisense molecule. Such compounds would have a molecular weight of about at least 4500 Da.

However, the issue of whether one skilled in the art would understand that these terms are directed to distinct molecules is rendered moot by the instant specification. Specifically, paragraph [0064] of the instant application as published states that "useful agents that inhibit one or more histone deacetylase isoforms, but less than all specific histone deacetylase isoforms, include antisense oligonucleotides and small molecule inhibitors." The specification goes on to state that in "certain preferred embodiments, the agent that inhibits the specific HDAC isoform is an oligonucleotide that inhibits expression of a nucleic acid molecule encoding a specific histone deacetylase isoform" (see paragraph [0067] of the instant application as published); and, alternatively, that "the agent of the first aspect of the invention may also be a small molecule inhibitor" (see paragraph [0083] of the instant application as published). Moreover, paragraph [0083] goes on to state that the term "small molecule" as used in reference to the inhibition of histone deacetylase is used to identify a compound having a molecular weight preferably less than 1000 Da.

Thus, it is clear that antisense oligonucleotides are distinct from the instantly claimed small molecule inhibitors. As such, one skilled in the art of small molecule chemistry would not have been motivated by the teachings of Taunton et al., Baracchini et al., and Bennett et al., alone or in combination, to do anything, much less to obtain the instantly claimed invention. Therefore, Taunton et al., Baracchini et al., and Bennett et al. are irrelevant to the instantly claimed invention. Accordingly, the question remains whether Claims 45-48 are patentable over Sambucetti et al.

Sambucetti et al., fail to teach or suggest the instantly claimed invention. Specifically, Sambucetti *et al.* teach that **total** histone deacetylase activity in whole cell extracts was completely inhibited by 1nM TPX (see first paragraph of Results section and Figure 1). Thus,

Claims 45-48 are patentable over Sambucetti et al. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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